Recommendations for the treatment of glomerular disease without established pathology

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RECOMMENDATIONS FOR THE TREATMENT OF GLOMERULAR DISEASE WITHOUT ESTABLISHED PATHOLOGY

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The prevalence of chronic kidney disease (CKD) in dogs may be as high as 1.5% of dogs presenting to general practice.[1] Glomerular disease may be the cause of renal injury in 50% or more of dogs with CKD.[2] Because glomerular diseases are common in dogs and the outcomes are not always favorable, there has been a recent enhanced effort to improve early recognition, diagnosis and treatment of all renal diseases in dogs, with particular emphasis on proteinuria renal diseases. In support of this effort, the WSAVA Renal Standardization Project has been working to develop a classification system for glomerular pathologic findings in dogs. At the same time, the International Renal Interest Society (IRIS) appointed a working group charged with developing clinical guidelines for the management of dogs with glomerular disease. The latter initiative used a formal consensus method for developing several sets of recommendations, including one set about the use of immunosuppressive therapy absent an established renal pathologic diagnosis.

There is no substitute for a pathologic diagnosis in the formulation of therapeutic plans for dogs with glomerular disease. However, in there are times when it is not possible to collect a renal biopsy specimen and the decision must be made whether or not to administer immunosuppressive agents to the affected dog. Four recommendations were derived and accepted at a high level of consensus to address this situation. These recommendations can help guide the decision about performing a renal biopsy in patients with proteinuria as well as the use of immunosuppressive drugs in those patients where the decision was made not to perform renal biopsy. [3]

Proteinuric dogs suspected of having glomerular disease should initially be managed using standard therapy and regular monitoring. However, this therapy rarely leads to complete remission of disease and, in some cases, adverse effects of the drugs used for standard therapy limit their use. When the targeted reduction in proteinuria (i.e., urine protein creatinine ratio <0.5 or a 50% reduction from baseline) is not achieved, and immunosuppressive or anti-inflammatory therapy is being considered, it is reasonable to readdress renal biopsy. When a renal biopsy cannot be obtained, the risk-to-benefit assessment for the patient should consider the arguments for and against using immunosuppressive drugs in dogs with proteinuria renal disease.

WHEN NOT TO PERFORM RENAL BIOPSY

Recommendation 1: *"Renal biopsy should not be performed in dogs (1) with IRIS CKD Stage 4; (2) when other medical contraindications are present and cannot be mitigated (including coagulopathy, renal cystic disease, moderate to severe hydronephrosis, pyelonephritis, perirenal abscess, uncontrolled hypertension, severe anemia, and pregnancy); or when results of renal biopsy are deemed unlikely to alter treatment, outcome, or prognosis."*[3]

Ideally, a renal biopsy would be evaluated in all dogs that are being managed for proteinuric renal disease. However, many times renal biopsy cannot be performed due to medical, practical, or financial limitations. In addition to the contraindications specifically stated in recommendation 1, relative contraindications to renal biopsy include available experienced personal to perform renal biopsy and the lack of access to a qualified and experienced renal diagnostic pathology center. Furthermore, if results of renal biopsy are deemed unlikely to alter treatment, outcome, or prognosis, then renal biopsy should not be recommended (e.g., end stage renal disease). Other factors that may preclude performing a renal biopsy include financial constraints or ethical concerns of the owner.

EXCLUSION CRITERIA FOR USING IMMUNOSUPPRESSIVE THERAPY

Recommendation 2: *"Immunosuppressive/ anti-inflammatory therapy should not be administered to dogs with proteinuria prior to renal biopsy when (1) proteinuria is not definitively glomerular in origin; (2) immunosuppressive therapy is otherwise contraindicated; (3) the dog breed and age of disease onset suggest that a nonimmune-mediated familial nephropathy is likely; or (4) amyloidosis is the most likely histopathologic diagnosis."*[3]

The first step in the decision process for using immunosuppressive therapy absent a renal biopsy is to verify that the proteinuria is of glomerular origin. When the source of proteinuria has not been definitively localized, immunosuppressive drugs are not indicated. Collective anecdotal experience of this consensus panel suggests that dogs with chronic tubulointerstitial disease rarely have UPC values greater than 2.0-3.0, although occasionally, acute kidney injury may transiently be associated with higher UPC results (i.e. $\geq$ 5.0). It is believed that UPC ranges from dogs with glomerular disease versus acute or chronic tubulointerstitial disease overlap, and results therefore must be interpreted in conjunction with other clinicopathologic findings when predicting type of disease. Therefore, dogs with UPC values less than 2.0 in conjunction with increased serum creatinine concentration and persistent isosthenuria or absence of proteinuria at the time of initial diagnosis of kidney disease should not receive treatment with immunosuppressive/ anti-inflammatory therapy without biopsy-supported evidence of active immune-mediated glomerular injury.

Immunosuppressive therapy should not be administered to dogs with concurrent illnesses for which immunosuppression is contraindicated (e.g., diabetes mellitus, hyperadrenocorticism, infectious diseases). Additionally, specific immunosuppressive drugs may be contraindicated with particular conditions (e.g. glucocorticoids in dogs with pancreatitis or uncontrolled hypertension, azathioprine in dogs with bone marrow suppression, hepatic dysfunction, or pancreatitis, etc.).

Immunosuppressive therapy should not be given to dogs that are likely to have a nonimmune-mediated familial nephropathy. Familial disease should be suspected when multiple related dogs are diagnosed with similar proteinuric renal disease or when a dog is diagnosed with proteinuric renal disease that is characteristic of a familial disease reported to occur in that breed. The diagnosis of familial nephropathy should be considered presumptive until confirmed by renal biopsy.

Although indirect evidence suggests that reactive amyloidosis in dogs is associated with a dysregulated immune response, immunosuppressive therapy in people and dogs is either of no benefit or may contribute to more rapid progression of disease.[4,5] There is too much overlap in UPC values between dogs with amyloidosis and dogs with other glomerulopathies to reliably use the UPC value to predict histopathologic diagnosis. However, renal amyloidosis may be more likely in dog with glomerular disease when the affected dog is of a breed known to be predisposed to amyloidosis (e.g., Shar pei,), additional clinical signs associated with hereditary amyloidosis in Shar peis are present (i.e., cyclical fever, distal joint effusion), or when amyloid deposition has been confirmed in other organs, particularly the liver.

WHEN IMMUNOSUPPRESSIVE THERAPY SHOULD BE CONSIDERED

Recommendation 3: *"Immunosuppressive drugs should be considered in dogs with glomerular disease that are being given standard therapy and do not have a biopsy-confirmed renal pathologic diagnosis when (1) serum creatinine is >3.0 mg/dL, or azotemia is progressive; or (2) hypoalbuminemia is severe (i.e., <2.0 g/dL)."*[3]

Evidence of immune complex glomerular disease was found in only 241 of 501 (48.1%) renal biopsies obtained from dogs suspected of having clinical evidence of glomerular disease.[6] In other words, 1 out of every 2 dogs with clinical evidence of glomerular disease would likely be candidates for immunosuppressive/ anti-inflammatory therapy. Clinical trials of immunosuppressive agents in dogs with specific glomerular diseases have not been reported, but in people with select glomerular diseases these drugs have a clear role. Because survival can be short in dogs with glomerular disease characterized by either azotemia or nephrotic syndrome and nearly 50% of dogs with clinical evidence of glomerular disease have immune-complex glomerular disease possibly responsive to immunosuppressive drugs, a therapeutic trial might be warranted in some dogs with glomerular range proteinuria absent a pathologic diagnosis.[7] Immunosuppressive therapy might be indicated in dogs with rapidly progressive disease, in spite of standard therapy, that either cannot be biopsied or that have been biopsied but results are not yet available. Specifically, aggressive immunosuppression may be considered if: 1) azotemia is acutely severe and/or progressive (i.e., creatinine > 5 mg/dl, IRIS AKI grades 4 or 5) at the time of diagnosis and there is no evidence of chronic disease; or, 2) hypoalbuminemia is severe (serum albumin < 2.0 g/dl)). In these situations, the protocols for peracute and rapidly progressive diseases should be followed. Likewise, immunosuppressive therapy might be indicated in dogs with chronic glomerular proteinuria if biopsy is not possible, neither age nor breed are indicative of familial renal disease, and other contraindications to immunosuppressive therapy are not present. In this situation, the protocols for more protracted disease should be followed. In all cases listed herein, immunosuppressive therapy should be considered a therapeutic trial; if there is no response after 8 to 12 weeks, therapy should be discontinued and the previous decision to not perform a renal biopsy should be revisited.

PROS AND CONS OF IMMUNOSUPPRESSIVE THERAPY ABSENT A PATHOLOGIC DIAGNOSIS

Recommendation 4: *"Immunosuppressive drugs should be administered to dogs in the absence of a renal pathologic diagnosis only after thorough client communication regarding the arguments for and against the use of these drugs in this setting. These agents should be administered cautiously, with close and careful patient monitoring."*[3]

Above all do no harm. Will we harm the patient by recommending an unproven immunosuppressive or anti-inflammatory treatment for a dog with glomerular disease that may not benefit from the therapy? Alternatively, canine glomerular disease can lead to serious complications or death and failure to provide a potentially helpful therapy may result in more harm than the potential risks of the therapy. Thus it is important to consider both the potential risks and potential benefits of recommending immunosuppressive/ anti-inflammatory treatment for dogs with clinical evidence of glomerular disease absent the findings of a renal biopsy. As previously stated, there is approximately a 50:50 chance that we would appropriately recommend immunosuppressive therapy for a dog with clinical evidence of glomerular disease absent a renal biopsy. Likewise, there is a 50:50 chance that recommending such therapy could be inappropriate for the patient without a biopsy and the patient is being put at-risk for developing one of the many potential side effects of these agents. The decision to proceed with therapy requires a case-by-case consideration of the risks of therapy.

The view that immunosuppressive therapy may be effective in improving clinical outcomes in dogs with some forms of glomerular disease is based on observations in people with glomerular disease as well as recent anecdotal evidence. Cyclosporine, the only drug that has been studied prospectively in dogs with glomerular disease, was found to have no detectable benefit.[8] However, dogs were included in this study regardless of renal pathologic diagnosis and the cyclosporine dose may have been too low. A treatment effect might have been found if only dogs with documented immune complex mediate glomerular disease were studied. No other studies of the use of immunosuppressive agents in dogs with glomerular disease have been published. As a consequence, it is difficult to predict a positive treatment effect with any accuracy.

REFERENCES

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